## REMARKS

### 1. STATUS OF THE CLAIMS

Claims 22-25, 27-36 and 45-52 are pending.

Claims 22, 32, and 45 have been amended by adding the recitation in step b)i) that the "temperature differential is produced by simultaneously heating said bottom with said heat source and cooling said top with said cooling means." Similar language is also included in new Claim 53 step c), new Claim 54 step c), and new Claim 55 c). Support is found in numerous places within the Specification (*e.g.*, at page 3, line 26, pages 5-6, and page 33, which describes Figure 5) and in the figures (Figure 5, left panel, which shows the simultaneous presence of a "hot end" and "cold end" along the height of one embodiment that uses a "plate"). Further support is in Figure 16 A, which shows a "water cooled top late" and a bottom "hot plate" simultaneously contacting opposite ends of a "sealed convection cavity" that contains the sample.

Claims 22, 32, and 45 have also been amended by adding the recitation in step b)ii) that the "heating produces spatially uniform temperature and temporally uniform temperature across said fluid in said top of said reaction vessel." Similar language is also included in new Claim 53 step c) i), new Claim 54 step c) i), and new Claim 55 step c) i). Support is in the Specification, paragraph bridging pages 32-33, which says

> "The fluid is heated from the bottom in such a way that the temperature of the bottom portion of the fluid remains relatively uniform **(spatial invariance)** and steady **(temporal invariance)**. Similarly it is assumed that the **top portion** also behaves in the same fashion so that the temperature gradient across the height also is uniform. This means, in other words, that a graph of Temperature vs. Time is a straight line (as shown)."

Claims 22, 32, and 45 have additionally been amended by adding the recitation in step b)iii) that the "cooling produces spatially uniform temperature and temporally uniform temperature across said fluid in said bottom of said reaction vessel." Similar language is also included in new Claim 53 step c) ii), new Claim 54 step c) ii), and new Claim 55 step c) ii). Support is in the Specification, paragraph bridging pages 32-33, as follows:

> "The fluid is heated from the bottom in such a way that the temperature of the **bottom portion** of the fluid remains relatively uniform **(spatial invariance)** and steady **(temporal invariance)**. . . . This means, in other words, that a graph of Temperature vs. Time is a straight line (as shown)."

Claim 45 has been additionally amended by changing "vessel" in step a)ii) to "vessels" in order to avoid potential lack of antecedent basis.

New Claims 53, 54 and 55 have been added to recite similar language to independent Claims 22, 32 and 45, respectively, with the exception that new Claims 53-55 do not recite the steps of transferring the reaction solution between different reaction vessels, that are recited in steps c) and d) of each of independent Claims 22, 32 and 45. Support is in the Specification, page 45, lines 4-7 that teaches:

> "Application of Rayleigh-Bénard convection flow principles to biological and biochemical reactions will allow for the efficient performance of reactions **without the necessity of transferring** small volumes of liquid or continually regulating and changing the temperature of the reaction vessel."[1]

Steps a) and b) of new Claims 53-55 are also supported by the same disclosure for steps a) and b) of independent Claim 22, 32, and 45, respectively. More specifically, support for Claim 53 steps a) and b) is the same as for Claim 22 steps a) and b); support for Claim 54 steps a) and b) is the same as for Claim 32 steps a) and b); and support for Claim 55 steps a) and b) is the same as for Claim 45 steps a) and b). Support for Claim 54 step c) iii) is the same as for Claim 32 step d). Support for Claim 55 step c) iii) is the same as for Claim 45 step d).

New Claims 56-61 have been added to recite that the "reaction vessel is selected from the group consisting of circular vessel and oval vessel." Support is in the Specification, page 4, lines 3-6 that teaches:

> "In yet another embodiment, the reaction chamber is **circular** or **oval** (*e.g.*, doughnut shaped with the doughnut standing on end, upright or vertically) with convection cycle traveling up one side of the circle (*i.e.*, up one side of the doughnut) and down the other."[2]

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1 Emphasis added.
2 Emphasis added.

**2. WIDHRAWN REJECTIONS**

Applicants note, with appreciation, the Examiner's withdrawal of each of the prior rejections[3] of

A. Claims 22-25 and 27-31 under 35 USC § 103(a) as allegedly being unpatentable over United States Patent Application Publication No. 2003/0077599 to Sogard in view of United States Patent No. 5,169,918 To Tomishima *et al.*,

B. Claims 32-54 under 35 USC § 103(a) as allegedly being unpatentable over United States Patent Application Publication No. 2003/0077599 to Sogard in view of United States Patent No. 5,169,918 To Tomishima *et al.*, and

C. Claims 47-50 under 35 USC § 102(b) as allegedly being anticipated by United States Patent Application Publication No. 2002/0127152 to Benett *et al.*

**3. NEW REJECTION OF CLAIMS 22-25, 27-29, 31-34, 36 AND 45-49 UNDER 35 U.S.C. § 103(a) OVER BENETT *et al.* IN VIEW OF PETERSEN *et al.*, AND RIRIE**

Claims 22-25, 27-29, 31-34, 36 and 45-49 stand rejected under 35 U.S.C. §103(a) over Benett *et al.* (U.S. Patent Application Publication No. 2002/0127152) in view of Petersen *et al.* (U.S. Patent No. 5,958,349), and Ririe (U.S. Patent Application Publication No. 2004/0209331).[4] Applicants respectfully disagree because a *prima facie* case of obviousness is lacking in view of the failure of the combined references to teach all the claims' limitations. In addition, even if a *prima facie* case of obviousness is arguably made, it is rebutted by the unexpectedly superior results taught by Dr. Ugaz's enclosed Declaration.

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[3] Office Action, page 2, item 2.
[4] Office Action, page 3, item 5.

**A. A *Prima facie* Case Of Obviousness Is Lacking Because The References Do Not Teach All The Claims' Limitations**

A *prima facie* case of obviousness requires the Examiner to cite to a combination of references that discloses all the elements of the claimed invention.[5] This is not the case with respect to at least the following 4 elements of the claims, thus entitling Applicants to withdrawal of this rejection.

i. **Aspect Ratio of Height to Diameter**

None of the references teaches the recited "aspect ratio of at least 3.3 wherein said ratio is defined as vessel height divided by vessel diameter." The Examiner correctly recognized that "Benett does not teach wherein the reaction vessels are configured with an aspect ratio of at least 3.3."[6] However, she mistakenly asserted that

> "Petersen *et al.* teaches a reaction vessel for heat-exchanging chemical processes having an **aspect ratio** of at least 2.1 (0009). Petersen *et al* teach an apparatus for thermal conductance having an **aspect ratio** of at least 2.1 or higher (see abstract and last paragraph of column 3)."[7]

The Examiner is respectfully reminded that the aspect ratio recited in the instant claims refer to the ratio of vessel **height** to vessel **diameter**. In contrast, Petersen *et al.* refers only to the ratio of **surface areas** and the ratio of thermal **conductance**. More specifically, Petersen *et al.* says that, for reaction vessels,

> "the total **surface areas** of the major surfaces be at least about twice that of the total **surface areas** of the minor surfaces to provide the desired **thermal conductance** ratio of 2:1."[8]

Since the Examiner relied solely on Petersen *et al.* to disclose the recited "aspect ratio," and since Petersen *et al.*'s ratios of surface area and of thermal conductance are **different** from the recited aspect ratio of height to diameter, Peterson *et al.* fails to teach this element of the claims. Thus, a *prima facie* case of obviousness is not established.

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5 *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).
6 Office Action, page 4, 2nd paragraph.
7 (Emphasis added) *Id.*
8 (Emphasis added) Petersen *et al.*, column 3, lines 54-58, and claims 1 and 2.

ii. **Producing a "Temperature Differential" by "Simultaneously" Heating and Cooling**

None of the references teaches the recited "temperature differential" that is produced by "simultaneously" heating the bottom and cooling the top of the reaction vessel." In particular, Benett *et al.* discloses systems for "convectively driven PCR thermal-cycling"[9] in which only a heater, but not the recited "cooling means," is used. For example, Benett *et al.* says that "Flow is generated by **heating** specific sections of the channel **11** and creating a convection cell or 'convective siphon.'."[10]

More particularly, Benett *et al.*'s Figures 1-3[11] and Figures 4 and 6[12] show that the sample **30** is held in a plastic sleeve or pouch **31** and clamped between two chamber halves **16** and **17** of a chamber unit **11**. The chamber unit **11** contains a heater (Depicted as element **15** of Figures 1-2) to heat the upper temperature zone (Depicted as element **13** of Figures 1-2, and element **43** of Figures 4 & 6). Benett *et al.*'s Figures 4-5[13] show an alternative configuration in which the sample **50**, rather than being clamped between two chamber halves, is instead introduced into the channels **42a, 42b, 42c**, and **42d** of Figure 4.[14] None of these configurations employ the instantly recited "**cooling means,**" much less the recited "**simultaneously heating**" and "**cooling.**"

Not only is Benett *et al.* silent on the use of the claimed inventions "cooling means," but it also **teaches away** from its use by directing the artisan to omitting a cooling means in order to reduce energy consumption. The Federal Circuit has said that discovering a method in the face of prior art that suggests that such a method would produce **unacceptable results** is the antithesis of obviousness.[15] Indeed, Benett *et al.* expressly states that its device

> "**eliminates** the need for **active cooling**"[16] [and] "**in the absence of active cooling**, heating and simmering account for virtually all of the power required."[17] "The objective is to incorporate real-time detection without sacrificing cycling speed or significantly increasing size or **power**

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9 Benett *et al.*, paragraph 0003.
10 Benett *et al.*, paragraphs 0040 and 0042 and Claim 26.
11 Benett *et al.*, paragraphs 0021-0026 and 0032-0034.
12 Benett *et al.*, paragraphs 0036-0042.
13 Benett *et al.*, paragraphs 0036-0042.
14 Benett *et al.*, paragraph 0041.
15 *In re Hedges*, 228 USPQ 685, 687 (Fed. Cir. 1986).
16 Benett *et al.*, paragraph 0026.
17 Benett *et al.*, paragraphs 0035 and 0050.

> **consumption**."[18] . . . "[I]mportant performance criteria for the device are cycling speed **power consumption** and size. . . . Power consumption is **extremely important** when designing portable PCR devices, and **critical** when designing a battery operated instrument."[19]

Petersen *et al.* also does not disclose the recited "temperature differential" and "simultaneous" heating and cooling, but instead only discloses in Figure 4 a cross sectional view of a vessel "in contact with heating elements and surrounded by a cooling chamber."[20]

Ririe is also silent on the recited "temperature differential" and "simultaneous" heating and cooling. Ririe discloses thermal cycling devices for temperature cycling of sample for DNA amplification in multiple reaction vessels.[21] Vessels containing a sample are inserted into an apparatus that has at least two heating elements in thermal contact with the vessel. The heating elements are set at different temperatures, with each temperature being optimal for different processes (*e.g.*, denaturation temperature, annealing temperature, or extension temperature).[22] Importantly, Ririe does not provide a "temperature differential" as recited in step b) because it does not **simultaneously** cool one side and heat an opposite side of the solution, but rather **sequentially** heats and cools the solution. Unlike the claimed invention, thermal cycling in Ririe's system is achieved by **mechanically** moving the solution between two temperature zones, rather than by the invention's **non-mechanical thermally-induced movement** of the solution between the top and bottom of the reaction vessel. For example, Ririe's heaters **26** and **27** are set at the same temperature to create an upper temperature zone **66** in mixture **16** within vessel **18**.[23] The mixture is incubated while all other heaters within other zones of the vessel are in the **closed position**. After incubation, the mixture is then **mechanically squeezed** into another portion of the same vessel where it comes into thermal contact with different heaters **25** and **28** that are set at a different temperature from heaters **26** and **27** to create a lower temperature zone **68** in mixture **16**. In other words, Ririe's solution is maintained

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[18] Benett *et al.*, paragraphs 0035 and 0050.
[19] Benett *et al.*, paragraph 0050.
[20] Petersen *et al.*, column 3, lines 3-5.
[21] Ririe, paragraph 0012.
[22] Ririe, paragraph 0013.
[23] Ririe, Figures 1A and 6, 0047.

at a single uniform temperature before being moved to a different part of the container to bring it to a different single uniform temperature. Thus, there is no "**temperature differential**" within Ririe's solution.

In view of the above, none of the references discloses the recited "temperature differential" and "simultaneously" heating the bottom and cooling the top of the reaction vessel." This, alone, negates a *prima facie* case of obviousness.

iii. **Spatial and temporal temperature uniformity at top**

Based on the above discussion of the cited prior art's disclosure, none of the references teaches the recited "heating produces spatially uniform temperature and temporally uniform temperature across said fluid in said **top** of said reaction vessel." This, without more, precludes establishing a *prima facie* case of obviousness.

iv. **Spatial and temporal temperature uniformity at bottom**

None of the references teaches the recited "cooling produces spatially uniform temperature and temporally uniform temperature across said fluid in said **bottom** of said reaction vessel." This omission negates a *prima facie* case of obviousness.

Because not just one, but **at least 4 of the claims' elements** are not taught or suggested by the prior art, this necessitates withdrawal of the rejection for alleged obviousness.

**B. Dr. Ugaz's Declaration Demonstrates That The Claimed Methods Provide Unexpectedly Superior Results**

Even if, for the sake of argument, a *prima facie* case of obviousness was made, it is rebutted by Dr. Ugaz's enclosed Declaration of unexpectedly superior results. Under the law,

"One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would

have found surprising or unexpected."[24]

Dr. Ugaz's Declaration provides data by Krishnan *et al.*[25] (Tab 1) that show that the methods of the instantly claimed invention have the unexpected superior property of yielding about a **10-fold reduction in reaction times** compared to prior art methods. This superior property was **unpredictable**, and was empirically determined.

Accordingly, a *prima facie* case of obviousness, if made is rebutted. Therefore, Applicants respectfully request withdrawal of the rejection of Claims 22-25, 27-29, 31-34, 36 and 45-49 under 35 U.S.C. §103(a) over Benett *et al.* in view of Petersen *et al.* and Ririe.

## 4. NEW REJECTION OF CLAIMS 30, 50 AND 51 UNDER 35 U.S.C. § 103(a) OVER BENETT *et al.* IN VIEW OF PETERSEN *et al.*, RIRIE AND SOGARD

Claims 30, 50 and 51 stand rejected under 35 U.S.C. §103(a) over Benett *et al.* (U.S. Patent Application Publication No. 2002/0127152) in view of Petersen *et al.* (U.S. Patent No. 5,958,349), Ririe (U.S. Patent Application Publication No. 2004/0209331), and Sogard (U.S. Patent Application Publication No. 2003/0077599).[26]

### A. A *Prima facie* Case Of Obviousness Is Lacking Because The References Do Not Teach All The Claims' Limitations

Applicants incorporate herein their above-discussed arguments in item 3.A. with respect to the rejection of Claims 22-25, 27-29, 31-34, 36 and 45-49 under 35 U.S.C. §103(a) over Benett *et al.* in view of Petersen *et al.* and Ririe. Specifically, none of these references discloses the recited (i) "aspect ratio of at least 3.3 wherein said ratio is defined as vessel height divided by vessel diameter," (ii) "temperature differential" that is produced by "simultaneously" heating the bottom and cooling the top of the reaction vessel," (iii) "heating produces spatially uniform temperature and temporally uniform temperature across said fluid in said top of said reaction vessel," and (iv) "cooling

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24 *In re Soni*, 34 USPQ2d 1684 (Fed. Cir. 1995).

25 Krishnan *et al.*, (2004) "Reactions And Fluidics In Miniaturized Natural Convection Systems," Anal. Chem. 76:6254-6265.

26 Office Action, page 6, item 6.

produces spatially uniform temperature and temporally uniform temperature across said fluid in said bottom of said reaction vessel." **Each** of these omissions, alone, negates a *prima facie* case of obviousness.

Sogard does not cure the above deficiencies. Sogard discloses methods for improving the stringency of hybridization of DNA oligonucleotide probes to a target DNA by covalently attaching the probes to a surface as an array, and contacting the array with target DNA under thermophoretic conditions[27] using a "temperature gradient of about 10° C./mm."[28] The temperature gradient is perpendicular to the array surface[29] and is used to drive the DNA samples toward the probe surface.[30] The temperature gradient is produced by placing the array and target DNA in a container and "two temperature control blocks" at opposite sides of the container.[31] Sogard also discloses that the where "the lower surface is warmer than the upper surface . . . Rayleigh-Benard may be retarded when the separation between the upper and lower surfaces is small, and when the temperature difference is small."[32] None of these disclosures provides the missing elements discussed in the preceding paragraph.

Because not only one, but **at least 4 of the claims' elements** are not taught or suggested by the prior art, Applicants respectfully request withdrawal of the rejection for alleged obviousness.

### B. Dr. Ugaz's Declaration Demonstrates That The Claimed Methods Provide Unexpectedly Superior Results

Applicants incorporate herein their above discussion in item 3.B. of Dr. Ugaz's Declaration with respect to the rejection of Claims 22-25, 27-29, 31-34, 36 and 45-49 under 35 U.S.C. §103(a) over Benett *et al.* in view of Petersen *et al.* and Ririe. In particular, the data referred to by Dr. Ugaz's Declaration demonstrates the unpredictable and surprising **10-fold reduction in reaction times** by the invention's claimed methods

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27 Sogard, paragraph 0013.
28 Sogard, paragraph 0014.
29 Sogard, paragraph 0013.
30 Sogard, paragraph 0042.
31 Sogard, paragraph 0041.
32 Sogard, paragraph 0043.

compared to prior art methods. Accordingly, even if a *prima facie* case of obviousness is arguably made, it is rebutted by the Declaration and evidence.

In view of the above, Applicants respectfully request withdrawal of the rejection of Claims 30, 50 and 51 under 35 U.S.C. §103(a) over Benett *et al.* in view of Petersen *et al.*, Ririe, and Sogard.

## CONCLUSION

Having addressed each of the rejections in the Office Action, Applicants believe that the claims are in condition for allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at (781) 828-9870.

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**Peter G. Carroll**
**Registration No. 32,837**

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105
(781) 828-9870, (415) 904-6500